Kardiovaskularni ishod i potencijalna dugoročna dobrobit renalne denervacije u bolesnika s rezistentnom hipertenzijom

Cardiovascular Outcomes and Potential Long-term Benefits of Renal Denervation in Patients with Resistant Hypertension

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SAŽETAK: Rezistentna hipertenzija (RH) nemogućnost je postizanja ciljnoga tlaka usprkos primijeni najmanje triju antihipertenzivnih lijekova različitih razreda u optimalnim dozama, od kojih jedan lijek mora biti diuretik. Prevalencija prave RH kreće se od 7,9 do 10 % liječenih hipertoničara te je povezana s povećanim rizikom od kardiorenovaskularnog oštećenja. Dodatno liječenje RH renalnom denervacijom indicirano je u bolesnika u kojih je kombiniranom farmakološkom terapijom nemoguće postići kontrolu arterijskoga tlaka uz prethodno dokazanu suradljivost i isključene sekundarne potencijalno lječive uzroke hipertenzije, bez anatomskih zapreka za renalnu denervaciju. Pojedinačni dokazi upućuju na pozitivni utjecaj renalne denervacije na očekivano trajanje života te prevenciju kardiovaskularnih komplikacija u bolesnika s RH koji imaju povišeni simpatički tonus poput bolesnika sa šećernom bolesti i bolesnika s kroničnom bubrežnom bolesti. Farmakoekonomske analize pokazuju da je kontrola hipertenzije lijekovima i metodama poput renalne denervacije jeftinija od liječenja komplikacija hipertenzivnog remodeliranja ciljnih organa.

SUMMARY: Resistant hypertension is the failure to achieve target blood pressure in spite of using a minimum of 3 antihypertensive drugs of different classes, one of which must be a diuretic, at maximal tolerated doses. The prevalence of true resistant hypertension ranges between 7.9-10.0% and is associated with higher risk of kidney and cardiovascular system damage. Treatment of resistant hypertension focuses on lifestyle modifications and pharmacological therapy. Device-based therapies are indicated in patients in whom pharmacological agents failed to control the blood pressure. Evidence suggests beneficial effects of renal sympathectomy on life expectancy and prevention of cardiovascular complications in patients with resistant hypertension with chronic activation of the sympathetic nervous system, such as chronic kidney disease and type 2 diabetes mellitus. In terms of costs, there is no question pharmacoeconomically that effective blood pressure control in resistant hypertension with drugs and new innovative devices therapies is cheaper than treating the consequences of hypertensive target organ damage.

KLJUČNE RIJEČI: rezistentna hipertenzija, kardiovaskularni rizik, renalna denervacija.

KEYWORDS: resistant hypertension, cardiovascular risk, renal denervation.

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Arterijska je hipertenzija najučestalija kronična bolest modernoga društva od koje boluje 30 – 45 % opće populacije, a udio se oboljelih povećava s dobi. U postojećim Smjernicama Europskog društva za hipertenziju / Europskog kardiološkog društva definirana je vrijednostima sistoličkoga tlaka više od 140 mmHg i dijastoličkoga tlaka više od 90 mmHg[1]. Dokazana je linearna veza između visine arterijskoga tlaka (AT) i kardiovaskularnih (KV) do-

Arterial hypertension is the most common chronic disease in modern society, affecting 30 – 45% of the general population, with the ratio increasing with age. The existing guidelines of the European Society of Hypertension/European Society of Cardiology define arterial hypertension as systolic pressure values above 140 mmHg and diastolic pressure above 90 mmHg[1]. A linear association has been demonstrated between blood pressure (BP)

gađaja kao što su moždani udar, infarkt miokarda, kronično zatajivanje srca i kronična bubrežna bolest (KBB). Rizik od KV mortaliteta udvostručuje se svakim porastom za 20/10 mmHg sistoličkog i dijastoličkog AT-a[2]. Arterijska je hipertenzija, u pravilu, udružena s dodatnim KV čimbenicima rizika poput šećerne bolesti, hiperlipidemije i pretilosti, koja poprima pandemijske razmjere[1].

Hipertenzija pri kojoj se unatoč primjeni minimalno triju vrsta antihipertenziva u optimalnim dozama, od kojih je jedan diuretik, i promjeni stila života ne mogu postići preporučene vrijednosti AT-a (<140/90 mmHg za opću populaciju i <130/80 mmHg za populaciju dijabetičara i pacijente s KBB-om) naziva se rezistentnom hipertenzijom (RH). Postizanje kontrole AT-a uz optimalne doze četiriju ili više antihipertenzivnih lijekova iz različitih skupina teško se postiže i održava[3,4]. Prevalencija prave RH danas se procjenjuje na 7,9 – 10 % svih hipertoničara[5,6]. Pacijenti s dijagnosticiranom RH imaju najmanje dvostruko veći rizik od oštećenja ciljnih organa, uključujući viši KV morbiditet i mortalitet, smanjenu bubrežnu funkciju i prisutnost endotelne disfunkcije, odnosno albuminuriju[7]. Liječenje hipertenzije primarno je usmjereno prema identifikaciji i promjeni rizičnih navika i stila života koje pridonose rezistenciji na terapiju. Prije postavljanja dijagnoze RH-a treba isključiti potencijalne sekundarne uzroke hipertenzije. Potrebno je izabrati (prema individualnim karakteristima i laboratorijskim nalazima) odgovarajuću kombiniranu antihipertenzivnu medikamentnu terapiju. Temeljni princip u liječenju RH jest blokada mehanizama koji uzrokuju povišenje AT-a, uključujući smanjenje ekspanzije volumena, blokadu aktivacije reninsko-angiotenzinsko-aldosteronskog sustava te periferne vaskularne rezistencije. Temeljna terapija pacijenata s RH uključuje blokadu reninsko-angiotenzinsko-aldosteronskog sustava, kalcijski antagonist i diuretik. Lijekovi bi trebali biti propisani u adekvatnoj dozi i odgovarajućim intervalima[7]. Kao četvrti lijek za liječenje RH-a danas se preporučuje uvođenje antagonista aldosterona. Aldosteron ima važnu ulogu u patogenezi RH-a svojim vazokonstrikcijskim učinkom i mijenjanjem propusnosti stijenki krvnih žila[8]. Lijekovi poput beta-blokatora preporučuju se kao peta linija lijekova, osim ako nisu indicirani prije s obzirom na prisutno kongestivno zatajivanje srca ili infarkt miokarda.

Spolne razlike i kardiovaskularni rizik bolesnika s rezistentnom hipertenzijom

Rezistentna hipertenzija često je udružena s oštećenjem ciljnih organa: razvojem hipertenzivne bolesti mozga, srca i bubrega te ima triputa veći rizik od razvoja hipertenzivnog oštećenja organa i KV komplikacija. Rizik je od razvoja RH-a veći u žena nego u muškaraca. To su žene koje češće pate od pretilosti, dislipidemije i šećerne bolesti te su starije dobi. Žene s RH imaju 1,4 puta veći rizik za ukupnu smrtnost u odnosu prema ženama s hipertenzijom koja je regulirana terapijom te 2,3 puta viši rizik nego žene bez hipertenzije. Žene s novodijagnosticiranom hipertenzijom imaju veći rizik od razvoja KBB-a, kao i veću učestalost te bolesti, a time i veći ukupni KV rizik[9] . Sniženje vrijednosti sistoličkog AT-a samo za 10 mmHg uzrokuje redukciju rizika od KV bolesti za 20 %, koronarne bolesti srca za 17 %, moždanog udara za 27 %, zatajivanja srca za 28 % te ukupne smrtnosti za 13 %[10]. Uspoređujući hipertoničare koji nemaju RH s onima koji imaju RH, populacija s RH ima višu prevalenciju komorbiditeta, i to

and cardiovascular (CV) events such as stroke, myocardial infarction, chronic heart failure, and chronic kidney disease (CKD). The risk of CV mortality doubles with every increase of 20/10 mmHg in systolic and diastolic BP[2]. Arterial hypertension is generally comorbid with other CV risk factors such as diabetes, hyperlipidemia, and obesity, the latter of which is reaching pandemic proportions[1].

Resistant hypertension (RH) is hypertension in which the recommended BP values (<140/90 mmHg for the general population and <130/80 mmHg for diabetics and patients with CKD) cannot be achieved despite the application of at least three types of hypertensives in optimal doses, one of which is a diuretic, and the application of lifestyle changes. BP control with optimal doses of 4 or more antihypertensive medications from different groups is hard to achieve and maintain[3,4]. The prevalence of true RH is today estimated at 7.9-10% of all patients with hypertension[5,6]. Patients with diagnosed RH have at least double the risk of target organ damage, including higher CV morbidity and mortality, reduced kidney function, and the presence of endothelial dysfunction or albuminuria[7]. Treatment of hypertension is primarily focused on identifying and changing risk-related habits and lifestyles, which contribute to resistance to therapy. Before establishing the diagnosis of RH, the potential secondary causes of hypertension must be excluded. The appropriate (based on individual characteristics and laboratory results) combined antihypertensive medication treatment must be chosen. The basic principle in the treatment of RH is blocking the mechanisms that lead to BP increase, including volume expansion reduction, peripheral vascular resistance, and blocking the activation of the renin-angiotensin-aldosterone system. The basic treatment for patients with RH includes blocking the renin-angiotensin-aldosterone system, a calcium antagonist, and a diuretic. Medication should be prescribed at adequate doses and in proper intervals[7]. Today, the introduction of an aldosterone antagonist as the fourth medication for the treatment of RH is recommended. Aldosterone has an important role in the pathogenesis of RH due to its vasoconstrictive effect and by changing vascular permeability[8]. Medication such as beta blockers are recommended as the fifth line of medication, unless they are indicated earlier due to the presence of congestive heart failure or myocardial infarction.

Sex differences and cardiovascular risk in patients with resistant hypertension

Resistant hypertension is often comorbid with target organ damage: the development of diseases of the brain, heart, and kidneys, and results in tripled risk of developing hypertensive organ damage and CV complications. The risk of developing RH is higher in women than in men. These are women that more frequently suffer from obesity, dyslipidemia, and diabetes and are of advanced age. Women with RH have a 1.4 times higher risk of total mortality in comparison with women with hypertension regulated by treatment as well as a 2.3 times higher risk in comparison with women without hypertension. Women with newly-diagnosed hypertension have a higher risk of developing CKD, a higher incidence of CKD, and consequently higher total CV risk[9]. Lowering systolic BP values by only 10 mmHg leads to a risk reduction for CV diseases of 20%, 17% for coronary diseases, 27% for stroke, 28% for heart failure, and total mortality reduction of 13%[10]. If we compare patients with hypertension who do not have RH to those with RH, the RH population

šećerne bolesti (48 % prema 30 % pri nerezistentnoj hipertenziji), KBB-a (45 % prema 24 %), ishemijske bolesti srca (41 % prema 22 %), cerebrovaskularnih bolesti (16 % prema 9 %, uz p<0,001)[11]. U populaciji pacijenata s RH potrebno je razlikovati dvije skupine: one koji imaju kontroliranu RH i drugu, češću, skupinu s nekontroliranom RH (61,7 %) i koja nosi veći rizik od razvoja oštećenja ciljnih organa (cerebrovaskularni je rizik 23 % veći, rizik od nastanka završnoga stupnja KBB-a je 25 % veći u usporedbi sa skupinom s kontroliranom RH)[11].

Priprema za renalnu denervaciju i ukratko o njoj

Kateterska renalna denervacija minimalno je invazivna metoda liječenja RH-a kojom se modulira tonus simpatičkoga živčanog sustava selektivnom ablacijom aferentnih i eferentnih simpatičkih živčanih vlakana obiju bubrežnih arterija. Procedura se provodi nepunih desetak godina, a postoji više od 1900 publikacija o renalnoj denervaciji od 2009. godine[12-18].

Postoji nekoliko sustava različitih proizvođača u svijetu koji se primjenjuju u izvođenju bubrežne denervacije, među kojima je najšire primjenjivan sustav *Symplicity Renal Denervation System*. Isporuka radiofrekventne energije na endoluminalnom dijelu renalne arterije vrši izvodi se elektrodom koja se nalazi na vrhu katetera. U prvotnim istraživanjima izvodila u nekoliko točaka (4 – 8 točaka) od distalnoga prema proksimalnom dijelu renalne arterije. Danas se postupak izvodi modernijim kateterom koji jednim dodirom isporučuje energiju na 4 točke, čime se skraćuje vrijeme postupka, a zbog manjega promjera ablacijskog katetera nova je metoda pogodna i za promjer renalnih arterija koje su manje od 4 mm (što je prije bila zapreka)[7,12-14]. Prvotna su istraživanja uključivala pacijente za postupak renalne denervacije ako su imali RH s vrijednostima sistoličkog tlaka ≥160mmHg (≥150mmHg u dijabetičara), unatoč liječenju najmanje trima antihipertenzivnim lijekovima različitih razreda u adekvatnim dozama, uključujući diuretik i modifikacije životnoga stila. U prvotnim istraživanjima (*SYMPLICITY HNT-1* i *HNT-2*) nije bio uključen kontinuirani mjerač arterijskoga tlaka[12-14]. Pacijenti su imali bubrežnu funkciju eGFR ≥ 45 mL/min/1,73 m^2 te renalne arterije odgovarajuće anatomije, odnosno promjera većeg od 4 mm[12]. Nakon prvotnih istraživanja koja su pokazala sigurnost i učinkovitost metode (postproceduralno sniženje AT-a za 27/17 mmHg nakon 12 mjeseci i 32/12 mmHg nakon 6 mjeseci) htjela se dokazati i učinkovitost u randomiziranom istraživanju, no studija *SYMPLICITY HNT-3* iz 2014. zbog niza proceduralnih problema nije dostigla cilj u smislu sniženja AT-a za više od 10 mmHg u odnosu prema kontrolnoj skupinu[15]. Danas je prije svakog postupka renalne denervacije potrebno potvrditi nekontroliranu RH kontinuiranim mjeračem tlaka tijekom 24 sata. Pseudorezistencija i sekundarna hipertenzija moraju biti isključene, potvrđena anatomska pogodnost za postupak, kao i potvrđena bolesnikova suradljivost ne samo mjerenjem broja tableta koje je bolesnik popio nego i određivanjem razine lijekova u krvi i/ili mokraći[19].

Najveći problem prvotnih istraživanja s renalnom denervacijom bila je ne samo heterogenost odgovora nakon renalne denervacije u smislu samog sniženja AT-a nego i veliki udio pacijenata koji su imali djelomičan (parcijalni) odgovor ili su bili „nonresponderi", odnosno uopće nisu imali nikakav učinak, što je razumljivo ako se prisjetimo patogenetskoga procesa regulacije AT-a[20]. Pojačana aktivnost simpatičkoga

has a higher prevalence of comorbidities, specifically diabetes (48% vs. 30% in non-resistant hypertension), CKD (45% vs. 24%), ischemic heart disease (41% vs. 22%), cerebrovascular disease (16% vs. 9%, p<0.001)[11]. Within the RH population, it is important to distinguish two groups: the group with controlled RH and the group with uncontrolled RH, which is larger (61.7%) and has a higher risk of developing target organ damage (cerebrovascular risk is higher by 23%, while the risk for end stage CKD is 25% higher in comparison with the controlled RH group)[11].

Preparation for renal denervation and a brief overview of renal denervation

Catheter renal denervation is a minimally invasive method for treating RH that modulates the tonus of the sympathetic nervous system by selective ablation of afferent and efferent sympathetic nerves of both renal arteries. The procedure has been practiced for less than a decade or so, and there have been more than 1900 publications on the topic of renal denervation since 2009[12-18].

There are several systems by different manufacturers around the world that are applied in performing renal denervation, among which the most widespread is the *Symplicity Renal Denervation System*. Delivery of radiofrequency energy to the endoluminal part of the renal artery is performed via an electrode at the tip of a catheter. In early studies it was delivered at several points (4-8) from the distal towards the proximal part of the renal artery. Today, the procedure is performed using a more modern catheter which delivers energy to 4 points with a single touch, reducing the duration of the procedure, and the smaller diameter of the catheter makes the new method appropriate for renal arteries with a diameter of less than 4 mm (which was an obstacle before)[7,12-14]. Early studies included patients for renal denervation procedures if they had RH with systolic BP values ≥160 mmHg (≥150 mmHg in diabetics) despite treatment with 3 antihypertensive medications of different classes in adequate doses, including a diuretic and lifestyle modification. The first studies (SYMPLICITY HNT-1 and HNT-2) did not include ambulatory blood pressure monitoring[12-14]. Patients had renal function eGFR≥45 mL/min/1.73 m^2 and renal arteries with appropriate anatomy, i.e. a diameter greater than 4 mm[12]. After the early studies demonstrated the safety and effectiveness of the method (postprocedural reduction of BP by 27/17 mmHg after 12 months and 32/12 mmHg after 6 months), demonstration of effectiveness in a randomized study was attempted, but the SYMPLICITY HNT-3 study from 2014, due to a number of procedural issues, did not demonstrate the target reduction in BP of more than 10 mmHg in comparison with the control group[15]. Today, uncontrolled RH must be confirmed before every renal denervation procedure using the 24-hour ambulatory blood pressure monitor. Pseudoresistant and secondary hypertension must be eliminated and anatomical suitability for the procedure must be confirmed, as must patient compliance not only by measuring the number of pills the patient consumes but also by determining medication levels in blood and/or urine[19].

The greatest problem of the early studies on renal denervation was not only the heterogeneity of responses after renal denervation in the reduction BP, but also a large ratio of patients who had a partial response to treatment or were nonresponders, i.e. the treatment did not have any effect, which is understandable if we consider the pathogenic process of BP regulation[20]. In-

živčanog sustava najčešći je, ali ne i jedini uzrok u podlozi hipertenzije. Sličan odgovor u smislu heterogenosti prisutan je uz propisivanje antihipertenzivnih lijekova[6,20]. Postoji nekoliko mogućih načina smanjenja varijabilnosti odgovora sniženja vrijednosti AT-a nakon renalne denervacije: kvaliteta samog postupka denervacije (novi kateteri koji omogućuju distalniju denervaciju gdje se nalazi većina simpatičkoga pleksusa, kao i iskusan interventni radiolog/kardiolog) te odabir pacijenata koji će imati dobrobit od dodatnog liječenja renalnom denervacijom[21]. U odabiru pacijenata za renalnu denervaciju danas se preporučuje odrediti krutost žila mjerenjem *pulse wave velocity* (PWV) koji je prediktor ukupne i KV smrtnosti, povezujući povišen PWV sa slabijim odgovorom na postupak renalne denervacije: povišen PWV utvrđen je u bolesnika starije dobi, s izoliranom sistoličkom hipertenzijom i dijabetičara[22].

Dugoročni ishodi renalne denervacije – pojedinačne istraživanja

Povećana simpatička aktivnost najčešći je podležeći čimbenik hipertenzije, zatajivanja srca, KBB-a, kao i poremećaja metabolizma glukoze[23]. Pojedinačna istraživanja pokazuju da bi renalna denervacija mogla biti dodatni učinkovit način smanjenja vrijednosti AT-a (svrha je renalne denervacije smanjiti vrijednost AT-a za 10 mmHg, a ne normalizacija AT-a) u osoba s RH te da ima i pozitivan učinak na kontrolu glukoze u krvi, funkciju srca, opstruktivnu apneju u snu te znakove oštećenja ciljnih organa[23-29]. Povećana aktivnost simpatikusa ima važnu ulogu i u patogenezi hipetrofije lijeve klijetke (HLK) i zatajivanja srca. Prisutnost HLK-a povezana je s povećanom učestalosti KV incidenata i smrti neovisno o drugim čimbenicima KV rizika i vrijednostima AT-a. S druge strane, regresija HLK-a poboljšava KV ishod[23]. Smanjenjem simpatičke preaktivnosti renalnom denervacijom smanjuje se i periferna vazokonstrikcija te periferni vaskularni otpor, čimbenici koji imaju važnu ulogu u razvoju zatajivanja srca. Regresija mase lijeve klijetke korelira sa stupnjem hipertrofije miokarda te je regresija znatnija u pacijenata s većim padom vrijednosti sistoličkoga tlaka.

Prema pojedinačnim izvješćima nakon renalne denervacije u bolesnika s kongestivnim zatajivanjem srca znatno se smanjila pojavnost ventrikularnih tahiaritmija, a, osim signifikantne redukcije AT-a u pacijenata koji su zbog fibrilacije atrija prethodno liječeni izolacijom plućnih vena, nakon renalne denervacije primijećeno je dodatno smanjenje broja epizoda fibrilacije atrija[26]. Dokazano je i smanjenje varijabilnosti AT-a nakon renalne denervacije[27].

Kronična aktivacija simpatičkoga živčanog sustava glavni je čimbenik koji pridonosi inzulinskoj rezistenciji i metaboličkom sindromu koji su povezani s centralnim tipom pretilosti i rizikom od razvoja šećerne bolesti. Uočen je pozitivan učinak nakon renalne denervacije na metabolizam glukoze u pacijenata oboljelih od RH u obliku smanjenja razina inzulina, C-peptida, HOMA-indeksa i glukoze. Stoga se smatra da bi renalna denervacija mogla usporiti ili čak zaustaviti progresiju inzulinske rezistencije u ovoj visoko rizičnoj skupini bolesnika[28].

Povećana simpatička aktivnost evidentna je i u ranim stupnjevima KBB-a i povezana je s pogoršanjem bubrežne funkcije, oštećenjem ciljnih organa te je čimbenik KV-a i ukupne smrtnosti u bolesnika sa završnim stupnjem KBB-a[29]. Albuminurija je važan neovisni prediktor KV-a i bubrežnih

creased activity of the sympathetic nervous system is the most common but not the only underlying cause of hypertension. A similar response regarding heterogeneity can also be observed in prescribing antihypertensive medication[6,20]. There are several potential ways of reducing the variability of responses in reduction of BP values after renal denervation: the quality of the procedure itself (new catheters allow more distal denervation where most of the sympathetic plexus is located, and the experience of the interventional radiologist/cardiologist also plays a role) as well as choosing patients who will benefit from additional treatment with renal denervation[21]. In choosing patients for renal denervation, the current recommendation is to determine arterial stiffness using pulse wave velocity (PWV) measurement, which is a predictor of total and CV mortality, associating elevated PWV with poorer response to renal denervation procedures: increased PWV was found in older patients, patients with isolated systolic hypertension, and diabetics[22].

Long-term outcomes for renal denervation – individual studies

Increased sympathetic activity is the most common underlying factor for hypertension, heart failure, CKD, and glucose metabolism disorder[23]. Individual studies have shown that renal denervation could be an additional effective method for reducing BP values (the goal of renal denervation is to reduce BP values by 10 mmHg, not to normalize BP) in persons with RH and that renal denervation had a positive effect on controlling blood glucose levels, heart function, obstructive sleep apnea, and signs of target organ damage[23-29]. Increased sympathetic activity also plays an important role in the pathogenesis of left ventricular hypertrophy (LVH) and heart failure. The presence of LVH is associated with increased incidence of CV events and death, irrespective of other CV risk factors and BP values. On the other hand, LVH regression improves CV outcomes[23]. Reducing sympathetic pre-activity by renal denervation also reduces peripheral vasoconstriction and peripheral vascular resistance, which are factors that have a significant role in the development of heart failure. Left ventricular mass regression correlates with the level of myocardial hypertrophy and is more significant in patients with a larger reduction in systolic pressure values.

Individual studies after renal denervation in patients with congestive heart failure found a significant reduction in the incidence of ventricular tachyarrhythmia, and in addition to BP reduction in patients who were previously treated for atrial fibrillation with pulmonary vein isolation, renal denervation also resulted in an additional reduction in the number of atrial fibrillation episodes[26]. A reduction of BP variability after renal denervation was also demonstrated[27].

Chronic activation of the sympathetic nervous system is the main factor contributing to insulin resistance and metabolic syndrome, which are associated with the central obesity and risk of developing diabetes. A positive effect was found after renal denervation on the glucose metabolism in patients suffering from RH, consisting of a reduction in levels of insulin, C-peptides, HOMA-index, and glucose. It is therefore believed that renal denervation could slow or even stop the progression of insulin resistance in this high-risk patient group[28].

Increased sympathetic activity is also evident in the early stages of CKD and is associated with deterioration of kidney function and target organ damage in addition to being a factor for CV and total mortality in patients with end stage CKD[29]. Albuminuria is a significant independent predictor for

bolesti te smrti u stanjima poput hipertenzije, bubrežne bolesti, šećerne bolesti, vaskularnih bolesti i u općoj populaciji. Albuminurija je linearno povezana s KV mortalitetom, odnosno postoji povezanost između povišene ekskrecije albumina urinom (>30 mg/d) i povišenih vrijednosti norepinefrina i epinefrina[30]. U studiji u kojoj je 59 pacijenata s RH i povišenim omjerom urinarnog albumina i kreatinina (UACR) podvrgnuto renalnoj denervaciji utvrđeno je da ona znatno smanjuje vrijednost UACR-a u pacijenata s mikroalbuminurijom i makroalbuminurijom[31]. Prevalencija mikroalbuminurije i makroalbuminurije bila je znatno smanjena 6 mjeseci nakon renalne denervacije[31]. Tri mjeseca nakon postupka renalne denervacije u bolesnika s KBB-om nije utvrđeno pogoršanja bubrežne bolesti nego je zamijećeno poboljšanje, odnosno porast glomerularne filtracije[32].

Opstruktivna apneja u snu (OSA) pogađa 3 – 7 % odrasle populacije te je povezana s povećanim rizikom od KV incidenata, uključujući moždani udar, zatajivanje srca, ishemijsku bolest srca i smrt[33]. Analizom utjecaja renalne denervacije na sistolički tlak u pacijenata s OSA ili bez nje te usporedbom s pacijentima iz kontrolne skupine u istraživanju *SYMPLICITY HTN-3* otkriveno je da su pacijenti s OSA liječeni renalnom denervacijom imali veći pad sistoličkoga tlaka nego pacijenti s OSA u kontrolnoj skupini. Osim toga, promjena maksimalnoga sistoličkog tlaka noću izražajnija je u pacijenata podvrgnutih renalnoj denervaciji. U kontrolnoj skupini uočeno je povećanje udjela pacijenata s *nondiping* uzorkom 6 mjeseci nakon početka istraživanja, ali takav trend nije bio prisutan u pacijenata s OSA u skupini liječenoj s renalnom denervacijom. Smanjenje aktivnosti simpatičkoga živčanog sustava renalnom denervacijom uzrokuje redukciju vrijednosti AT-a i stupnja OSA, a utvrđeno je i smanjenje apneja-hipopneja indeksa, indeksa desaturacije kisika, *Epworth Sleepiness Scale score* i koncentracije glukoze u plazmi[34]. S obzirom na to da se nakon postupka renalne denervacije uočavaju pozitivni učinci i na pridružene bolesti poput šećerne bolesti, KBB-a, metaboličkog sindroma i OSA sindroma, koji su često udruženi s RH koja je češća u žena, klinička korist od ovoga terapijskog postupka mnogo je veća te zahtijeva dugoročnije praćenje ishoda u sada definiranoj populaciji pacijenata kojima je potrebno prethodno odrediti krutost žila s pomoću PWV-a[35], koja je prediktor ishoda dodatnog liječenja renalnom denervacijom[36]. Farmakoekonomske analize pokazuju da je kontrola hipertenzije lijekovima i metodama poput renalne denervacije jeftinija od liječenja komplikacija hipertenzivnog remodeliranja ciljnih organa poput kronične srčane slabosti i liječenja dijalizom[37]. Postupak renalne denervacije smanjuje desetogodišnji relativni rizik (za moždani udar 0,70/0,83; infarkt miokarda 0,68/0,85; koronarnu bolest srca 0,78/0,90; srčano popuštanje 0,79/0,92; završni stupanj KBB-a 0,72/0,81) i povećava preživljenje[37].

Zaključak

U pojedinačnim izvješćima nakon renalne denervacije uočeno je poboljšanje višestrukih čimbenika rizika za KV bolesti, kao i KBB. Postupkom renalne denervacije dokazano je smanjenje proteinurije te ponovna uspostava cirkadijalnog ritma. Doprinos renalne denervacije smanjenju ukupnog KV rizika varira između različitih skupina pacijenata pa je stoga iznimno bitno napraviti probir pacijenata, ovisno o pridruženim čimbenicima rizika, koji će imati najveću korist od samog postupka renalne denervacije.

CV and kidney diseases as well as death in conditions such as hypertension, kidney disease, diabetes, vascular disease, and the general population. Albuminuria is linearly associated with CV mortality, and there is an association between increased urine secretion of albumin (>30 mg/d) and elevated values of norepinephrine and epinephrine[30]. A study in which 59 patients with RH and increased urine albumin-to-creatinine ratio (UACR) were subjected to renal denervation found that it significantly reduced UACR values in patients with micro- and macroalbuminuria[31]. The prevalence of microalbuminuria and macroalbuminuria was significantly reduced 6 months after renal denervation[31]. Three months after renal denervation in patients with CKD, there was no deterioration in kidney disease but rather an improvement in the form of improved glomerular filtration[32].

Obstructive sleep apnea (OSA) affects 3-7% of the adult population and is associated with increased risk of CV events, including stroke, heart failure, ischemic heart disease, and death[33]. Analysis of the effects of renal denervation on systolic pressure in patients with and without OSA and comparison with patients from the control group in the SYMPLICITY HTN-3 study found that patients with OSA treated with renal denervation had a greater reduction in systolic pressure than patients in the OSA control group. Additionally, the change in systolic BP during the night was more pronounced in patients subjected to renal denervation. In the control group, the ratio of patients with nondipping had increased 6 months after the start of the study, but this trend was not observed in patients with OSA in the group treated with renal denervation. The reduction in the activity of the sympathetic nervous system through renal denervation leads to a reduction in BP pressure values and OSA levels, and a reduction of the apnea-hypopnea index, oxygen desaturation index, Epworth Sleepiness Scale score, and plasma glucose concentration was also observed[34]. Given that positive effects have been observed after renal denervation even regarding associated diseases such as diabetes, CKD, metabolic syndrome, and OSA syndrome, which are often comorbid with RH, which is more common in women, the clinical benefits of this treatment procedure are significantly higher and require more long-term outcome monitoring in a now defined population of patients who should undergo previous arterial stiffness measurement using PWV[35], an outcome predictor for additional treatment for renal denervation[36]. Pharmacoeconomic analyses show that hypertension control though medication and methods such as renal denervation is cheaper than treating complications of hypertensive target organ remodeling such as chronic heart failure and dialysis treatment[37]. Renal denervation reduces 10-year relative risk (0.70/0.03 for stroke; 0.68/0.85 for myocardial infarction; 0.78/0.90 for coronary artery disease; 0.79/0.92 for heart failure; 0.72/0.81 for end-stage renal disease) and improves survival[37].

Conclusion

Individual studies on renal denervation have found improvements in multiple risk factors for CV diseases and CKD. Renal denervation has been demonstrated to reduce proteinuria and reestablish circadian rhythm. The contribution of renal denervation to total CV varies between different groups of patients, so it is extremely important to perform patient selection depending on the associated risk factors in order to choose patients who will benefit most from renal denervation.

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